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NUTRITION REVIEWS

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VITAMINS AND ANTIBODIES

A great deal has been written concerning the possible relationships between nutrition and resistance-susceptibility to infection. A number of review papers have periodically assessed the voluminous and controversial literature on this subject (S. W. Clausen, *Physiol. Rev.* **14,** *309 (1934)*; E. C. Robertson, *Medicine* **13,** *123 (1934)*; W. L. Aycock and G. E. Lutman, *Am. J. Med. Sci.* **208,** *389 (1944)*; H. A. Schneider, *Vitamins and Hormones* **4,** *35 (1946)*; P. F. Clark *et al.*, *Bact. Rev.* **13,** *99 (1949)*; Schneider, *Am. J. Trop. Med.* **31,** *174 (1951)*).

The mechanism of resistance or susceptibility to infection involves numerous factors, many of which are but poorly understood. The classic antigen-antibody reaction is generally considered to be a significant facet of this complex phenomenon. This is particularly true in the case of "acquired" resistance or immunity where the host responds to the infectious agent or to an immunologically active fraction thereof by the production of antibodies. Although most of the studies on the significance of nutritional factors have dealt with "natural" resistance, it would appear appropriate to inquire into the interdependence, if any, between nutrition and the process of actively acquired immunity.

P. R. Cannon and his school have stressed the importance of protein nutrition in antibody synthesis and resistance to infection. Their views, as well as the contrasting opinions of others, have appeared frequently in this journal. In the present paper, attention will be directed to the effects of specific vitamin deficiencies upon antibody production in experimental animals.

The older researches on the relationship between vitamin intake and antibody fabrication in experimental animals are summarized in the various reviews cited above. An examination of this literature reveals a mass of conflicting data with no unequivocal evidence to indicate that any specific vitamin deficiency invariably leads to an impaired antibody production. Much of this work was done before the era of modern nutrition and in many cases the lack of adequate controls is evident. Accordingly, it becomes difficult to evaluate the specificity of many of the observed effects in the light of present day nutritional knowledge.

More recently, a failure to observe any effects of individual vitamin deficiencies upon humoral antibody response has been noted (H. Natvig, *Nutrition Abstr. Rev.* **12,** *198 (1942/43)*; H. E. Wilson *et al.*, *J. Am. Med. Assn.* **121,** *1411 (1943)*; I. Ruchman, *J. Immunology* **53,** *51 (1946)*; W. B. Leftwich and G. S. Mirick, *J. Exp. Med.* **89,** *155 (1949)*). Contrasting results have, however, been obtained by others. L. J. Berry, J. Davis, and T. D. Spies (*J. Lab. Clin. Med.* **30,** *684 (1945)*) demonstrated a decreased antibody production in rats fed a nutritionally inadequate diet similar to that consumed in an area of endemic malnutrition. Supplementation of this diet with casein, minerals, and the B vitamins stimulated antibody synthesis. The effects of single vitamin deficiencies were not studied. The data presented by J. Y. C. Watt (*Am. J. Hyg.* **39,** *145 (1944)*) indicated a diminished antibody response to *N. muris* in thiamine and riboflavin deficiencies. P. A. Little, J. J. Oleson, and P. K. Roesch (*J. Immunology* **65,** *491 (1950)*) have observed that pteroylglutamic acid deficiency inhibited the agglutinin response of chicks to various bacterial antigens. A diminished antibody response to the rickettsiae of murine typhus fever has been reported by K. Wertman and J. L. Sarandria (*Proc. Soc. Exp. Biol. Med.* **76,** *388 (1951)*; **78,**

332 (1951); Wertman, F. D. Crisley, and Sarandria, *Ibid.* **80,** *404 (1952)*), in rats maintained on pantothenic acid-, thiamine-, pyridoxine-, riboflavin- and folacin-deficient diets. These experiments emphasized the significance of the dosage of immunizing agent in determining the antibody response in certain deficiency states.

Of particular significance in this field is the work of H. C. Stoerk and his collaborators. Working with well-defined deficiency states and utilizing adequate controls, these workers demonstrated a striking impairment of the antibody response to sheep erythrocytes in pyridoxine-deficient rats. Deficiencies in thiamine, riboflavin, or pantothenic acid failed to influence antibody production (Stoerk and H. N. Eisen, *Proc. Soc. Exp. Biol. Med.* **62,** *88 (1946)*; Stoerk, Eisen, and H. M. John, *J. Exp. Med.* **85,** *365 (1947)*). A. E. Axelrod, B. B. Carter, R. H. McCoy, and R. Geisinger (*Proc. Soc. Exp. Biol. Med.* **66,** *137 (1947)*), utilizing human erythrocytes as the antigenic stimulus, were able to confirm the decreased antibody response in pyridoxine-deficient rats. In addition, these workers observed an equally severe impairment of antibody production in pantothenic acid deficiency and a moderate inhibition in riboflavin deficiency. This discrepancy, particularly in the case of pantothenic acid deficiency, may be attributed to the fact that the human erythrocytes utilized by Axelrod and his co-workers furnish a far stronger antigenic stimulus for hemagglutinin production in the rat than do the sheep erythrocytes employed by Stoerk *et al.* It is possible, therefore, that pantothenic acid and riboflavin do not become limiting factors for hemagglutinin production when the antigenic stimulus (sheep erythrocytes) is of low magnitude. In a subsequent paper, P. P. Ludovici, Axelrod, and Carter (*Ibid.* **72,** *81 (1949)*) noted decreased antibody titers in rats fed a pantothenic acid-deficient diet for only three weeks prior to immunization. This deleterious effect of a relatively mild deficiency renders it unlikely that the difference between the two laboratories can be resolved on the basis that Stoerk and his co-workers limited their observations to a relatively mild pantothenic acid deficiency. Continued experimentation by the Pittsburgh group has furnished convincing proof for the role of pantothenic acid in antibody formation.

The relationship between vitamins and antibodies has been extended to include the effects of deficiencies of thiamine, biotin, pteroylglutamic acid, niacin-tryptophan, vitamin B_{12}, vitamin A and vitamin D upon the hemagglutinin response of the rat to the antigenic stimulus of human erythrocytes (B. B. Carter and A. E. Axelrod, *Proc. Soc. Exp. Biol. Med.* **67,** *416 (1948)*; P. P. Ludovici and Axelrod, *Ibid.* **77,** *526 (1951)*). Identical immunologic procedures were employed throughout these investigations. From these results, it was possible to classify roughly the effects of these deficiencies upon circulating antibodies into three groups as follows: Group I, severe impairment of antibody response (pantothenic acid, pyridoxine and pteroylglutamic acid deficiencies); Group II, moderate impairment of antibody response (riboflavin, thiamine, biotin, vitamin A and niacin-tryptophan deficiencies); Group III, no impairment of antibody response (vitamin B_{12} and vitamin D deficiencies). Ludovici and Axelrod (*Ibid.* **77,** *530 (1951)*) have also shown that panthenol [alpha, gamma-dihydroxy - N - (- 3 - hydroxypropyl) - beta, beta-dimethyl butyramide], the alcohol analogue of pantothenic acid, is as efficacious as pantothenic acid in promoting antibody synthesis in pantothenic acid-deficient rats. These results are in accord with previous studies demonstrating the quantitative conversion of panthenol to pantothenic acid in the rat.

During the course of these studies on the relationship of nutritional status to antibody

formation, the above authors have had occasion to observe instances where the dietary requirements of a given factor for growth did not parallel its need for antibody synthesis. Thus, methionine was capable of sparing the requirement of pantothenic acid for antibody synthesis, but not for growth (P. P. Ludovici, A. E. Axelrod, and B. B. Carter, *Proc. Soc. Exp. Biol. Med.* **76,** *670 (1951)*). In contrast, supplementation of a niacin-tryptophan-low diet with niacin produced a marked growth response without any effect on the lowered titer of circulating antibodies. Supplementation of this diet with tryptophan promoted both growth and antibody synthesis (*loc. cit.*). Limitations of space do not permit a discussion of these interesting relationships. Of significance to the nutritionist, however, is the observation that the process of antibody synthesis may represent a more sensitive criterion of dietary adequacy than that of growth and, as such, may be used to advantage in the evaluation of nutritional state.

The recognition of the significant role of certain vitamins in establishing a high level of humoral antibodies following antigenic stimulation brings into focus the question of their mode of action. First, are the effects of these vitamin deficiencies actually a nonspecific response to the inanition which is always present in such deficient animals? This question may be answered in the negative. In the experiments of Stoerk *et al.*, Axelrod *et al.*, and Wertman *et al.*, the utilization of sufficient inanition controls, both of the paired-weighed as well as the paired-fed type, has eliminated any significant effects of inanition. Further, no parallelism exists between the degree of inanition and the extent to which the antibody response is depressed. Thus, the observed effects may be attributed directly to the absence of the specific vitamin involved. Secondly, is the action of the vitamin primarily concerned with its function in the production and maintenance of the antibody-synthesizing cells of the organism? Stoerk and co-workers have observed that pyridoxine deficiency resulted in marked lymphoid atrophy. Since a relationship between lymphocytes and antibodies had been suggested, these workers were led to investigate the effect of a pyridoxine deficiency upon antibody production. As stated above, a marked effect of this vitamin deficiency was observed. However, as the authors state, such observations do not prove that the suppression of the serum antibodies was a consequence of the lymphoid atrophy. They consider it possible that both alterations may occur independently in pyridoxine deficiency. A causal relationship between the loss of lymphocytes in pyridoxine deficiency and impairment of the antibody response becomes even less probable as the result of the observation by Stoerk *et al.* that the extreme lymphoid atrophy due to advanced thiamine deficiency was not associated with impairment of immune responses (*loc. cit.*).

The final answer to this question of a relationship between the vitamins and the antibody-fabricating cells will not be obtained until it is known with certainty which cells of the body produce antibodies and what effect a specific vitamin deficiency has upon such cells. Thirdly, it must be recognized that the *serum* antibody level probably reflects an equilibrium state which is determined on the one hand by the rates of synthesis and release of the antibody, and on the other by its rate of destruction. Thus, a decreased antibody titer in the serum cannot be taken as unequivocal proof for the actual impairment of antibody synthesis. The effects of a vitamin deficiency upon the factors of antibody distribution and degradation must be evaluated before a definite relationship between vitamin and antibody synthesis can be established. In addition, the possibilities that the vitamin deficiency may cause ex-

cessive destruction of the introduced antigen or an impairment in the ability of the antibody-forming apparatus to take up antigens must be considered. These factors have been evaluated by H. C. Stoerk (*Ann. N. Y. Acad. Sci.* **52,** *1302 (1950)*) and P. P. Ludovici, A. E. Axelrod, and B. B. Carter (*Proc. Soc. Exp. Biol. Med.* **76,** *665 (1951)*), and both groups of workers concluded that it is probable that pyridoxine and pantothenic acid function in the process of antibody synthesis.

The pronounced effect of a pteroylglutamic acid deficiency response is comparable with that noted in a pantothenic acid deficiency state. The observation of L. D. Wright and A. D. Welch (*J. Nutrition* **27,** *55 (1944)*) that the utilization of pantothenic acid may be dependent upon the presence of pteroylglutamic acid suggests that the action of pteroylglutamic acid upon antibody synthesis may be mediated through its effect upon pantothenic acid metabolism. Further experimentation will be required to determine whether pteroylglutamic acid plays a direct or indirect role in the processes of antibody fabrication.

Thus, the available evidence would indicate that certain B vitamins, notably pyridoxine, pantothenic acid and pteroylglutamic acid, play a significant role in antibody synthesis. There is considerable basis for linking pyridoxine to amino acid metabolism, and its participation in antibody production may be related to this function. A corresponding mechanism for the action of pantothenic acid has not yet been demonstrated. A relationship between pantothenic acid and peptide bond formation is suggested by the observation of H. Chantrenne (*J. Biol. Chem.* **189,** *227 (1951)*) that coenzyme A, a compound which contains pantothenic acid, is involved in the synthesis of hippuric acid. The function of coenzyme A in the metabolism of "active two-carbon" units is rapidly being unfolded. The suggestion that acetyl amino acids may be involved in the biologic formation of peptide bonds invites speculation on the role of coenzyme A and the "active two-carbon" units in antibody synthesis. This postulated interrelationship between pantothenic acid and amino acid metabolism is of interest in view of the pantothenic acid-sparing action of methionine on antibody formation (*loc. cit.*).

The need for certain vitamins in the attainment of a normal immune response has been established in specified instances. The precise function of these vitamins, notably pyridoxine, pantothenic acid, and pteroylglutamic acid, has not been determined with certainty. Available evidence, albeit indirect in nature, favors the concept that these vitamins are directly concerned in antibody synthesis.

The significance of these relationships to the general problem of nutrition and resistance-susceptibility to infection is obscure. Clarification will follow the demonstration that the immune response to the infectious agent is markedly affected in a given vitamin deficiency state and that this change in immune response is a vital factor in determining the resistance and susceptibility to the infection.

In recent years, a number of specific vitamin antagonists have been synthesized. The utilization of these compounds to inhibit the undesirable synthesis of certain antibodies, *e.g.*, Rh antibodies, suggests itself. Obviously, the deleterious nature of these antagonists to the host would be a serious deterrent to their use and these compounds would be of value only if their activity could be confined essentially to the antibody-synthesizing tissues. Stoerk has already demonstrated the ability of desoxypyridoxine, a pyridoxine antagonist, to inhibit an immune response (*loc. cit.*). The extension of such studies to other vitamin antagonists offers interesting possibilities.

The ability to control antibody produc-

tion by regulating the vitamin intake should be a useful tool in the unraveling of the mechanisms of antibody synthesis. Since antibodies represent a class of specialized proteins, such studies would yield information regarding the processes of protein anabolism in general. The fact that the measurement of antibodies is greatly facilitated by the application of specific immunologic procedures renders them particularly suitable for studies of protein synthesis.

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NOTE

A Balanced Diet

A booklet recently published by The Nutrition Foundation is entitled "A Balanced Diet." What is a balanced diet? Why should it be balanced? What is being balanced? A balanced diet is simply a variety of foods which supply all of the nutrients needed for good health and supply these nutrients in their proper amounts and in proper relation to each other. A diet should be balanced because such a diet provides better nutrition than an unbalanced diet. A well-balanced diet is also more economical because of the fact that it is better utilized, less is wasted by the body, and the net result is better health.

Section captions in this booklet are: the nutrients to be balanced, water, fiber, suggestions for balanced meals, translating nutrients into balanced meals, the energy balance, desirable weights, hot vs. cold foods, how to balance the meals for all age groups, pregnancy and lactation, old people, hints for good diets.

The booklet concludes: "A diet varied in food intake at each meal, properly prepared and consumed in such quantities as to obtain and maintain desirable weight, will generally be a balanced diet. This diet should include all of the protective foods such as meat, fish, milk, eggs, fruits, vegetables, enriched and whole grain breads and cereals. A balanced diet is important for good health because nutrition is an important factor in the growth, function, maintenance, and repair of all the cells of the body. As such, it is the most important environmental factor affecting health. Every citizen interested in improved health from a purely personal basis or from a national or international point of view should be interested in, know something about, and practice better nutrition."

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The Nutrition Foundation was organized by food and related manufacturers in December, 1941, as a sincere expression of their interest in scientific progress and human health. The basic purposes of the Foundation are: (1) the development of a comprehensive program of fundamental research, providing basic information in the science of nutrition; and (2) the support of educational measures that will assist in making the science of nutrition effective in the lives of present and future generations.

The publication of NUTRITION REVIEWS has been undertaken to enable professionally trained people to keep abreast of current progress and to have available an unbiased, authoritative review of the current research literature in the science of nutrition.

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